UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

008059

AUG 13 1990

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Tebuthiuron - Acute Toxicity Studies
Caswell No. 366A
MRID. No. 405839-01 thru 405839-04
HED Project No. 0-938

FROM: Elizabeth A. Doyle, Ph.D. Elizabeth A. Doyle 8/2/90
Review Section I, Tox Branch II (HFAS) (H7509C)

TO: Carol Peterson, PM 74
Special Review and Reregistration Division (H7508C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Tox Branch II (HFAS) (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief 8/9/90
Tox Branch II (HFAS)
Health Effects Division (H7509C)

Registrant: Eli Lilly and Company

Action Requested: Review of acute toxicity studies provided by the registrant for tebuthiuron technical.

The following summary of the data is provided:

1) Acute oral LD_{50} = 477.5 mg/kg in male rats and 387.5 mg/kg in female rats. Toxicity Category II. MRID No. 405839-01. Minimum

2) Acute Dermal LD_{50} > 5000 mg/kg in male and female rabbits. Toxicity Category IV. MRID No. 405839-02. Guideline

3) Primary Dermal Irritation - Essentially nonirritating to male and female rabbit skin. Toxicity Category IV. MRID No. 405839-02. Guideline

4) Primary Ocular Irritation - Slightly irritating to the eyes of male and female New Zealand White rabbits. Toxicity Category IV. MRID No. 405839-03. Guideline

5) Dermal Sensitization - Not a sensitizer in female guinea pigs. MRID No. 405839-04. Guideline

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Reviewed by: Elizabeth A. Doyle, Ph.D. Elizabeth A Doyle 8/6 90
Section I, Toxicology Branch II (HFAS) (H7509C)
Secondary reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I. 8/6/90
Section I, Toxicology Branch II (HFAS) (H7509C)

DATA EVALUATION REPORT

Study Type: Primary Eye Irritation - Rabbit (81-4) **Tox. Chem. No.:** 366A

MRID Number: 405839-03

Test Material: Tebuthiuron

Synonyms: N-[5-(1,1-dimethylethyl)-1,3,4-thiadoazol-2-yl]-N'N-dimethylurea

Study Number(s): B02688

Sponsor: Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

Testing Facility: Toxicology Division
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

Title of Report: The acute primary ocular irritation of technical tebuthiuron in the New Zealand White rabbit

Author(s): D. S. Negilski and G. L. Rock

Report Issued: March 23, 1988

Conclusions: Tebuthiuron is only slightly irritating in the eyes of male and female New Zealand White rabbits.

Toxicity Category IV

Classification of Data: Core - Guideline

This study satisfies the guideline requirements (81-4) for a "Primary Ocular Irritation Study in Rabbits".

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MATERIALS AND METHODS

The subject test material for this study was technical tebuthiuron (purity = 99.1%, Lot No. 729AS7).

Three male and three female New Zealand White rabbits were obtained from Lesser's Rabbitry, Union Grove, Wisconsin. At the initiation of the study, the rabbits were 12 to 18 weeks of age. Body weights were 3.63 ± 0.14 kg and 3.82 ± 0.25 kg for male and female rabbits, respectively. The animals were acclimated to the laboratory for two weeks prior to treatment. Twenty-four hours prior to initiation of the study, the eyes of the rabbits were examined visually using a binocular loupe. Sodium fluorescein was used to assist in identification of corneal injury.

One eye of each animal was treated with 67 mg of test material (approximate equivalent volume = 0.1 cc). The untreated eye served as the control. The test material was placed into the conjunctival cul-de-sac and the eyelids were held closed for several seconds to prevent expulsion of the test material.

Eyes were examined and graded for lesions at 1, 24, 48 and 72 hours after dosing and again at seven days. Sodium fluorescein was instilled into the eyes at the 24 hour observation. Individual body weights were recorded at the initiation of the study and at seven days.

RESULTS AND DISCUSSION

Irritation due to the test material was minimal, consisting only of slight conjunctival hyperemia which was present in all treated eyes at one hour after treatment (All scores = 1). Scores were "0" by 24 hours after treatment. All eyes were completely cleared by 48 hours after treatment.

CONCLUSIONS

Tebuthiuron was essentially nonirritating in the eyes of male and female New Zealand White rabbits.

Toxicity Category IV

CLASSIFICATION

Core - Guideline

This study satisfies the guideline requirements (81-4) for a "Primary Ocular Irritation Study in Rabbits".

Reviewed by: Elizabeth A. Doyle, Ph.D. Elizabeth A. Doyle 8/6/90
Section I, Toxicology Branch II (HFAS) (H7509C)
Secondary reviewer: Yiannakis M. Ioannou, Ph.D. 8/6/90
Section I, Toxicology Branch II (HFAS) (H7509C)

DATA EVALUATION REPORT

Study Type: Acute Oral Toxicity - Rats Tox. Chem. No.: 366A

MRID Number: 405839-01

Test Material: Tebuthiuron

Synonyms: N-[5-(1,1-dimethylethyl)-1,3,4-thiadoazol-2-yl]-N'N-dimethylurea

Study Number(s): R06188 and R06288

Sponsor: Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

Testing Facility: Toxicology Division
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

Title of Report: The acute toxicity of technical tebuthiuron administered orally to the Fischer 344 rat.

Author(s): D. S. Negilski and D. R. Hawkins

Report Issued: March 23, 1988

Conclusions: The oral LD_{50} of tebuthiuron in males is 477.5 mg/kg and in females is 387.5 mg/kg.

Toxicity Category II

Classification: Core - Minimum
(Deficient in that the doses selected for females in this study were too high.)

This study satisfies the guideline requirements (81-1) for an "Acute Oral Toxicity Study in Rats".

MATERIALS AND METHODS

The test material for this study was technical tebuthiuron (purity = 99.1%, Lot No. 729AS7).

Twenty male and 20 female F344/NHsd rats were obtained from Harlan-Sprague, Dawley, Inc., Indianapolis, Indiana. They were acclimated to the laboratory for 48 hours prior to treatment. At initiation of treatment, they were eight to nine weeks old. Males weighed 166.5 ± 6.30 g and females weighed 134.0 ± 7.88 g. Rats were randomly assigned to treatment groups, with 5/sex/dose in each group. Prior to treatment, the rats were fasted for a minimum of 16 hours.

On the first day of treatment, rats were given single oral doses of 365, 500, 700 and 1000 mg/kg. The test material was prepared as a 100 mg of test material per ml in a 10% aqueous acacia solution. The final concentration was achieved by further dilution with 10% aqueous acacia solution.

Rats were observed hourly for the first seven hours, then daily for the next 15 days. Mean body weights were calculated on days 8 and 15 posttreatment. A gross pathologic examination was conducted at the end of the study on all surviving animals, and included evaluation of general body condition, external orifices, and tissues and organs from the thoracic and abdominal cavities.

RESULTS AND DISCUSSION

No deaths occurred in males from the 365 mg/kg treatment group. Mortality occurred in all treatment groups for females. All deaths occurred by day 4 posttreatment.

MORTALITY (#/5 treated)

	Dose (mg/kg)			
	365	500	700	1000
Males	0	4	5	5
Females	2	5	5	5

Clinical signs recorded during the posttreatment period included ataxia, hypoactivity, lethargy, coma, tremors, chromodacryorrhea, clonic convulsions and poor grooming. Males also exhibited chromorhinorrhea, hunched posture and pale eye color. By day 6 posttreatment, survivors appeared normal. Mean body weight gains for males from the 365 mg/kg group were 25 and 64 g, and from the 500 mg/kg group were -25 and 20 g for days 8 and 15, respectively. Mean body weight gains for female from the 365 mg/kg group were 13.3 and 25 g at days 8 and 15, respectively.

Rats that died on test exhibited blood congestion or hemorrhage of the upper gastrointestinal tract, lung, urinary bladder and thymus. Bladder distension was indicated by the registrant to be due to increased urinary output. Pale liver and dehydration were indicated to be late occurring effects and may have been due to terminal hemodynamic changes. No abnormal findings were reported for rats that survived to terminal sacrifice.

The acute oral LD_{50} for males was calculated to be 477.5 mg/kg and for females was calculated to be 387.5 mg/kg.

The only noteworthy deficiency in this study was the improper dose selection for females as indicated by the deaths in the low dose group. However, the data provided are adequate for assignment of this test material to a toxicity category.

CONCLUSIONS

The oral LD_{50} of tebuthiuron in males is 477.5 mg/kg and in females is 387.5 mg/kg.

Toxicity Category II

CLASSIFICATION

Core - Minimum
(Deficient in that the doses selected for females in this study were too high.)

This study satisfies the guideline requirements (81-1) for an "Acute Oral Toxicity Study in Rats".

Reviewed by: Elizabeth A. Doyle, Ph.D. Elizabeth A. Doyle 8/6/90
Section I, Toxicology Branch II (HFAS) (H7509C)
Secondary reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I. 5/6/90
Section I, Toxicology Branch II (HFAS) (H7509C)

DATA EVALUATION REPORT

Study Type: Dermal Sensitization - Guinea Pigs (81-6)

Tox. Chem. No.: 366A

MRID Number: 405839-04

Test Material: Tebuthiuron

Synonyms: N-[5-(1,1-dimethylethyl)-1,3,4-thiadoazol-2-yl]-N'N-dimethylurea

Study Number(s): G01088

Sponsor: Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

Testing Facility: Toxicology Division
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

Title of Report: A dermal sensitization study of technical tebuthiuron in guinea pig

Author(s): D. S. Negilski and G. L. Rock

Report Issued: March 23, 1988

Conclusions: Tebuthiuron is not a sensitizer in female guinea pigs under the conditions of this study.

Classification of Data: Core - Guideline

This study satisfies the guideline requirements (81-6) for a "Dermal Sensitization Study in Guinea Pigs".

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MATERIALS AND METHODS

Female Hartley albino guinea pigs were obtained from Charles River Laboratories, Inc., Portage, Michigan 49081. Following a two week aclimation period, 27 animals were selected for use in the study. At the initiation of the study, the animals were four to seven weeks old and weighed 381 ± 20.6 g. Animals were given food (Purina Guinea Pig Chow Diet No. 5026) and water ad libitum.

The test material used in this study was technical tebuthiuron (purity = 99.1%) (Lot No. 729AS7). 1-Chloro-2,4-dinitrobenzene (Sigma Chemical Company, Lot No. 82F-0036) was used as the positive control.

During the induction phase of the study, twelve guinea pigs were patched with the test material (50 mg) and six with DNCB (0.2 ml of 0.1% DNCB w/v in 70% ethanol) three times per week for two consecutive weeks. The animals were then allowed a ten day rest period, after which the twelve induced guinea pigs and six naive guinea pigs were challenged with the test material and the six induced positive control guinea pigs and three naive guinea pigs were challenged with DNCB. Challenge applications were made to naive sites.

Prior to each patching, the nuchal area was prepared by clipping the hair and swabbing the exposed skin with acetone immediately prior to treatment. The acetone wash was intended to cause a slight disruption in barrier integrity and to remove extraneous lipid material that might inhibit percutaneous absorption. The test material was applied to the gauze portion of a Band-Aid (1.5 cm square area) and applied to the nuchal area with occlusive adhesive tape. At the end of the six hour exposure period, the patch was removed and excess material was brushed off.

Treated sites were observed at 24 hours after each induction and challenge treatment and at 48 and 72 hours after each challenge treatment for erythema and edema.

Body weights were recorded at the initiation of the study and weekly thereafter.

RESULTS

All guinea pigs survived the study.

Dermal irritation did not occur in animals patched with the test material during the induction phase of the study except for erythema with a score of 1 (minimal) in one animal after the second induction treatment. DNCB caused moderate to severe erythema and slight to moderate edema in all guinea pigs after the fourth induction treatment, and severe erythema and moderate to severe edema following the fifth induction application.

No evidence of sensitization due to the test material occurred after the challenge application. The DNCB induced guinea pigs exhibited slight to moderate erythema and edema 24 hours after challenge. Erythema and edema persisted at the 48 and 72 hour readings. Naive animals patch at challenge

with the test material or DNCB had no scores except "0" for erythema or edema.

CONCLUSION

Tebuthiuron is not a sensitizer in female guinea pigs under the conditions of this study.

CLASSIFICATION

Core - Guideline

This study satisfies the guideline (81-6) requirements for a "Dermal Sensitization Study in Guinea Pig".

Reviewed by: Elizabeth A. Doyle, Ph.D. Elizabeth A. Doyle 8/6/90
Section I, Toxicology Branch II (HFAS) (H7509C)
Secondary reviewer: Yiannakis M. Ioannou, Ph.D. J.M.I. 8/6/90
Section I, Toxicology Branch II (HFAS) (H7509C)

DATA EVALUATION REPORT

Study Type: Acute Dermal Toxicity - Rabbits (81-2) Tox. Chem. No.: 366A
and Primary Dermal Irritation - Rabbits (81-5)

MRID Number: 405839-02 003059

Test Material: Tebuthiuron

Synonyms: N-[5-(1,1-dimethylethyl)-1,3,4-thiadoazol-2-yl]-N'N-dimethylurea

Study Number(s): B02088

Sponsor: Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

Testing Facility: Toxicology Division
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, Indiana 46140

Title of Report: The acute dermal toxicity and primary irritation of technical tebuthiuron in the New Zealand White rabbit

Author(s): D. S. Negilski and G. L. Rock

Report Issued: March 23, 1988

Conclusions: Based upon this study, 1) the dermal LD_{50} for tebuthiuron in male and female rabbits is >5000 mg/kg, and 2) tebuthiuron is essentially nonirritating to the skins of male and female rabbits.

Acute Dermal Toxicity Category: IV
Primary Dermal Irritation Toxicity Category: IV

Classification of Data: Core - Guideline

This study satisfies the guideline requirements (81-2 and 81-5) for an "Acute Dermal Toxicity Study in Rabbits" and a "Primary Dermal Irritation Study in Rabbits".

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MATERIALS AND METHODS

The subject test material for this study was technical tebuthiuron (purity = 99.1%, Lot No. 729AS7).

Five male and five female New Zealand White rabbits were obtained from Lesser's Rabbitry, Union Grove, Wisconsin. At the initiation of the study, the animals were 12 to 18 weeks of age and weighed 3.50 ± 0.28 kg and 3.22 ± 0.16 kg for males and females, respectively. Rabbits were provided with food (Purina Rabbit Chow No. 5325) and water ad libitum.

The fur was clipped from the back of each rabbit. The test material was applied at a dose of 5000 mg/kg to the back of each animal on a damp nonocclusive dressing. The dressing and test material were secured in place with 24 hours with an elastic sleeve. Residual treatment material was rinsed off with warm water. Collars were placed on the rabbits and remained in place for 48 hours to prevent licking of the treatment sites.

One hour after removal of the dressing and daily for the next 14 days, the rabbits were examined for signs of toxicity. Individual body weights were recorded on the day that the test material was applied and weekly thereafter. Treated skin was graded for irritation daily.

The study was terminated at day 14, and a gross pathologic examination was conducted on all rabbits. The carcasses were evaluated for general condition externally, for orifices; tissues and organs in the thoracic and abdominal cavities were also examined.

RESULTS AND DISCUSSION

No mortality occurred during the study and no overt signs of toxcity were reported. The dermal LD_{50} for tebuthiuron in male and female rabbits is >5000 mg/kg. All rabbits gained weight during the study. Body weight gains in males and females for the 14-day postexposure period were 162 and 172 g, respectively.

Primary irritation scores recorded in these rabbits were "N", or no perceptible effects for all times of observation except for the 24-hour reading, at which time scores of "B1", or barely perceptible erythema were recorded for three rabbits. By the 48-hour observation, all evidence of irritation had cleared.

The study deviates from the guideline requirements for a primary dermal irritation assay in that a 6-hour exposure is specified. However, this deviation is not considered to compromise the interpretability of the irritation score because 1) the exposure was more, not less, severe than specified, and 2) no overt toxicity occurred which would in any way confound the outcome of a primary dermal irritation evaluation.

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CONCLUSIONS

Based upon this study, 1) the dermal LD_{50} for tebuthiuron in male and female rabbits is >5000 mg/kg, and 2) tebuthiuron is essentially nonirritating to the skins of male and female rabbits.

Acute Dermal Toxicity Category: IV
Primary Dermal Irritation Toxicity Category: IV

CLASSIFICATION

Core - Guideline

This study satisfies the guideline requirements (81-2 and 81-5) for an "Acute Dermal Toxicity Study in Rabbits" and a "Primary Dermal Irritation Study in Rabbits".